REMARKS

This timely filed Reply is responsive to the Office Action dated June 26, 2006. Claims 1-15 and 21 were pending at the time of the Office Action. Claims 16-20 and 22-33 were previously withdrawn pursuant to a Restriction Requirement.

In the Office Action claims 1-3, 8-11, 13 and 14 are rejected under 35 U.S.C. §102(b) as being anticipated by Nazarenko et al. (U.S. Patent No. 6,117,635 A), as evidenced by a chapter in a book by Lakowicz entitled "Principles of Fluorescence Spectroscopy", Second Edition, pgs. 25-61, 1999. Claims 4-7, 12, 15 and 21 are determined to be allowable if rewritten in independent form.

In this Reply, the specification has been amended to resolve the sequence issues and claims 1-3, 8, 9, 10 and 14 have been amended. No new matter has been added.

The present invention extends the flourescence based non-Raman based assaying techniques using stem-loop oligonucleotide probes referred to as "molecular beacons" first disclosed by Tyagi to Raman spectroscopy, specifically to Surface Enhanced Raman Spectroscopy (SERS). As described in paragraph 61 of the present application (portion copied below), significantly, probes according to the invention are superior to conventional fluorescence-based molecular beacons because Raman spectroscopy based on the present invention using the new claimed probes provides a much better multiplex advantage.

For example, 100 Raman labels may be used with SMP according to the invention instead of 3-4 labels in fluorescence. Improved multiplex capability of Raman/SMP over fluorescence results because individual fluorescent lines are generally 50 to 200 nm wide at room temperature, while a SERS assay using SMP 100 results in a line width which is substantially less than 1 nm. The Raman/SERS line width is defined by the laser line width which is generally much less than 1 angstrom and the spectral resolution of the spectrometer or detector system which can have a comparable spectral resolution.

Claim 1 has been amended to clarify the present invention and emphasize the SERS aspect, which is well known to rely on certain selected solid metal comprising nanoparticle surfaces. Specifically, the class of metals particles that are SERS active are metals for which surface plasmons are excited by visible radiation, such as Cu, Ag and Au as noted below in the present application. As amended, the nanoparticle limitation now recites "at least one solid nanoparticle ~~having at least a~~ comprising an elemental metal, said nanoparticle having an outer surface ~~component"~~.

Applicant has copied paragraphs 16-19 of the present application which describes the SERS effect and the requirements for the obtaining same, and provides clear support for the claim amendment shown above.

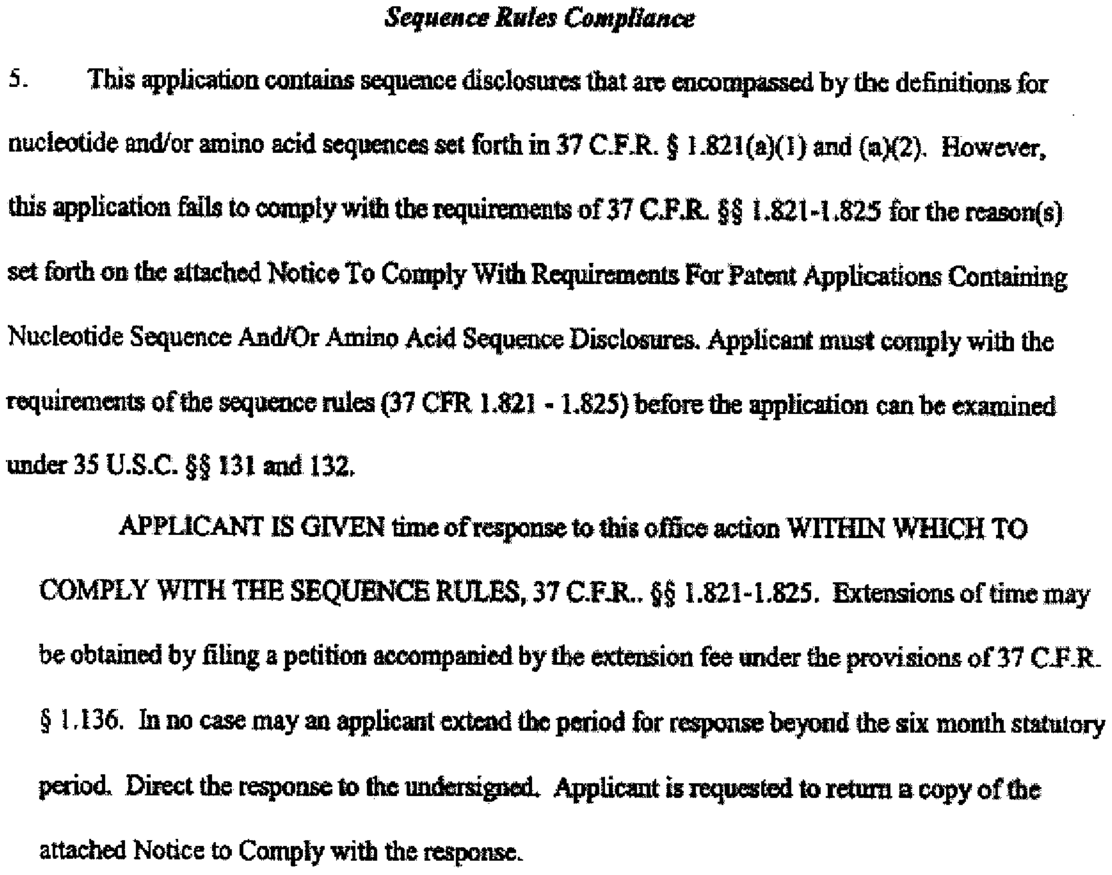
[0016] Raman spectroscopy is complementary to fluorescence, and has been used as an analytical tool for certain applications due to its excellent specificity for chemical group identification. However, low sensitivity historically has limited its applications. Recently, the Raman technique has been rejuvenated following the discovery of a Raman enhancement of up to 10^6 to 10^{10} for molecules adsorbed on microstructures of metal surfaces. The technique associated with this phenomenon is known as surface-enhanced Raman scattering (SERS) spectroscopy. The enhancement is due to a microstructured metal surface scattering process which increases the intrinsically weak normal Raman scattering (NRS) due to a combination of several electromagnetic and chemical effects between the molecule adsorbed on the metal surface and the metal surface itself.

[0017] The enhancement is primarily due to plasmon excitation at the metal surface. Thus, the effect is generally limited to Cu, Ag and Au, and to a few other metals for which surface plasmons are excited by visible radiation. Although chemisorption is not essential, when it does occur there may be further enhancement of the Raman signal, since the formation of new chemical bonds and the consequent perturbation of adsorbate electronic energy levels can lead to a surface-induced resonance effect. The combination of surface- and resonance-enhancement, often referred to as surface-enhanced resonance Raman scattering (SERRS) can occur when adsorbates have intense electronic absorption bands in the same spectral region as the metal surface plasmon resonance, yielding an overall enhancement as large as 10^{10} to 10^{12}.

[0018] Nanoparticles can comprise solid metal of nanoscale size or nanoparticles coated with metal layers. Nanospheres of dielectric materials coated with a thin layer of silver (metal nanoshell) have been found to be SERS active. Nanospheres of magnetic materials coated with a thin layer of metal can also be used as SERS-active magnetic nanoparticles. The core diameter and the metal thickness of nanoshells can be varied to modify the SERS properties of the nanoparticles as disclosed in an article co-authored by the inventor. [R. L. Moody, T. Vo-Dinh, and W. H. Fletcher, "Investigation of Experimental Parameters for Surface-Enhanced Raman Spectroscopy," Appl. Spectrosc., 41, 966 (1987)].

Applicant also notes that paragraphs 21, 22, 43, 45, 46, 51, 52, 54, 55, 60, 62, 68-70, 78, 80, 82, 87, 93, 96 and 100 provide further description of metal comprising nanoparticles according to the invention including repeated teachings of a metal comprising nanoparticle surface and in a preferred embodiment a metallic surface. Metal nanoparticles are well known to be solid particles having elemental (non-ionic) metal atoms bound together, typically in a highly ordered structure, such as in a crystal lattice. (also, paragraph 18 which discloses "solid metal").

In the Office Action the Examiner indicated that the application does not comply with the sequence listing requirements of 37 C.F.R. §1.821(a)(1) and (a)(2) (copied below).



Sequence Rules Compliance

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

APPLICANT IS GIVEN time of response to this office action WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R.. §§ 1.821-1.825. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

> The specification contains sequences without SEQ ID NOs on page 14, paragraph [0044] and on page 30 in paragraphs [0091]-[0093]. In an amendment filed February 24, 2004, Applicant amended paragraphs [0093]-[0095] to include SEQ ID NOs. However, paragraphs [0094] and [0095] do not contain any SEQ ID NOs. If the sequences in paragraphs [0044] and [0091]-[0093] are already present in the previously submitted sequence listing, the paragraphs need to be amended to include the SEQ ID NOs. However, if these sequences are not present in the sequence listing on file, a new paper and electronic copies of the sequence listing need to be provided.

In response, Applicant has provided the required sequence listing information along with the Notice to Comply that accompanied the Office Action. Accordingly, the application now complies with the sequence listing requirements of 37 C.F.R. §1.821(a)(1) and (a)(2).

Turning now to claim rejections based on cited art, According to the Examiner:

> 16. Claims 1-3, 8-11, 13 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Nazarenko et al. (U.S. Patent No. 6,117,635 A), as evidenced by Lakowicz (Principles of Fluorescence Spectroscopy, Second Edition, pp. 25-61, 1999).
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> Regarding claim 1, Nazarenko et al. teach an oligonucleotide with stem-loop structure, where both stems have fluorescent labels attached to them, with one of the labels being a fluorescence acceptor and the other a donor (Fig. 1; col. 12, lines 51-67; col. 13, lines 1-3; col. 14, lines 22-33; col. 15, lines 46-67; col. 16, lines 1-6; col. 17, lines 46-67; col. 18; col. 19, lines 1-10; co. 20, lines 17-56). Since every nucleotide sequence is complementary to at least one target nucleic acid, the loop of the primer of Nazarenko et al. anticipates this limitation. One of the labels used is a lanthanide chelate, which contains a lanthanide ion (col. 17, lines 46-62), therefore, since the size of the lanthanide ion is about 0.1 nm, the chelate anticipates the limitation of a nanoparticle having at least a metal component. Finally, in case when the two stems are outfitted with a fluorescent donor and acceptor, separation of the two during amplification will lead to weaker signal from the primer when it is hybridized to the target than the signal emitted before it was incorporated into the target (col. 15, lines 24-28; col. 20, lines 52-64).

Nazarenko is entitled " Nucleic acid amplification oligonucleotides with molecular energy transfer labels and methods based thereon" and discloses labeled nucleic acid amplification oligonucleotides, which can be linear or hairpin primers or blocking oligonucleotides. The oligonucleotides are labeled with donor and/or acceptor moieties of molecular energy transfer pairs. The moieties are generally fluorophores, such that fluorescent energy emitted by the donor is absorbed by the acceptor. The acceptor may be a fluorophore that fluoresces at a wavelength different from the donor moiety, or it may be a quencher.

Nazarenko does not once Raman, SERS and any derivative or Raman. The Nazarenko disclosure is based entirely on solution based methods. "Solution" is disclosed throughout the disclosure. "Particle" or any similar or related term is not mentioned once. The lanthanide ion label cited by the Examiner that is disclosed by Nazarenko as a "metal" is clearly a single metal ion chelated in solution. As such, it is clearly not Applicant's as amended claimed solid nanoparticle, does not include the claimed elemental metal, and since it is not a particle, does not have the claimed outer surface characteristic of a particle. Accordingly, Applicant's claimed oligonucleotide-based surface-enhanced Raman spectroscopy molecular probe (SMP) comprising:

at least one *solid nanoparticle comprising an elemental metal, said nanoparticle having an outer surface,* and

at least one pin loop, said pin loop including a loop sequence complementary to at least one target sequence, a first stem attached to one end of said pin loop having at least one SERS active label attached thereto and a second stem attached to the other end of said pin loop and said nanoparticle, wherein said probe generates a stronger SERS signal upon irradiation with excitation radiation when not bound to said target sequence as compared to a SERS signal following hybridization of said probe with said target sequence, evidences an inventive step and is thus patentable over the cited art. Although several of the dependent claims recite independently patentable limitations, due to patentability of claim 1 Applicant will not address this matter.

The Raman detection system recited in claim 10 has been amended to recite the oligonucleotide-based surface-enhanced Raman spectroscopy molecular probe (SMP) recited in amended claim 1. On this basis alone, amended claim 10 and its respective dependent claims are patentable over the cited art.

Applicants have made every effort to present claims which distinguish over the cited art, and it is believed that all claims are in condition for allowance. However, Applicants invite the Examiner to call the undersigned if it is believed that a telephonic interview (direct line (561) 671-3662) would expedite the prosecution of the application to an allowance. Although no fee is believed to be due, the Commissioner for Patents is hereby authorized to charge any deficiency in fees due or credit an excess in fees with the filing of the papers submitted herein during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,
AKERMAN SENTERFITT

Date: 12/01/06

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Docket No. 6321-227